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Conscious Sedation Medication Choice Does Not Affect Outcomes After Transcatheter Aortic Valve Replacement

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Conscious Sedation Medication Choice Does Not Affect Outcomes After Transcatheter Aortic Valve Replacement

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In Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

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CONSCIOUS SEDATION MEDICATION CHOICE DOES NOT AFFECT OUTCOMES AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT.

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Conscious Sedation (CS) has become a mainstay option for anesthesia in Transcatheter Aortic Valve Replacement (TAVR), but there has been limited investigation into the effect of CS medication choice on patient outcomes. This study aimed to assess whether the CS medications used in TAVR were associated with primary outcomes, including hospital length of stay (LOS), mortality, or need for post-operative permanent pacemaker. This retrospective, observational study included 272 patients who underwent TAVR with CS at a tertiary teaching hospital between September 2014 and December 2017. Patient and procedure data were collected from the STS/ACC Transcatheter Valve Therapy Registry and chart review. Patients were grouped according to the CS medications they received during TAVR, and three analyses were conducted from the pool of 272 patients: *Propofol versus No propofol* (n=203 vs. n=64), *Propofol plus midazolam versus Propofol only* (n=70 vs. n=94), and *Dexmedetomidine versus No dexmedetomidine* (n=86 vs. n=186). Several patient and procedure characteristics differed significantly at baseline in all three analyses. Regression and Cox proportional hazard analyses were conducted to adjust for differences. After adjustment, primary outcomes were not significantly different in each analysis, and there were no differences in secondary outcomes, including in-hospital death, discharge location, creatinine change, hemoglobin change, discharge creatinine, and incidence of blood transfusion. Among patients with prolonged LOS, more patients in the Propofol plus midazolam group had hypotension as a causative factor compared to the Propofol only group (56% versus 17%, $p = 0.075$), even though the Propofol plus midazolam group was

younger and less ill. Ultimately, it is unclear whether CS medication choice for TAVR affects patient outcomes, and it is possible that medication selection can be left to provider preference. Further analysis with larger sample sizes may be warranted, especially to study the effect of propofol plus midazolam compared to single-sedative regimens.

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INTRODUCTION

Aortic stenosis (AS) is the most prevalent valvular disease in developed countries,[1] affecting an estimated 12-13% of patients who are ≥ 75-years old.[2] In the United States alone, an estimated 2.5 million people over the age of 75 suffer from AS.[3] AS patients are sub-classified into "at risk," "progressive," or "severe" based on diagnostic criteria including patent valve area, pressure gradient, maximum aortic velocity, ventricular dysfunction, and other measures.[4,5] It is estimated that more than 25% of all current AS cases are severe, and the number of severe AS cases increases year over year; an estimated 27,000 patients newly meet criteria for severe AS annually.[2] Severe AS can either be asymptomatic (~25%) or symptomatic (~75%),[2] and symptoms include exertional dyspnea and angina, sequelae of heart failure, and syncope or presyncope.[5] Without treatment, roughly 50% of symptomatic, severe AS patients die within 2 years, and the prognosis continues to worsen thereafter.[6-9] Since there is no medical therapy available for severe AS, replacement of the diseased valve is crucial. Replacement can be accomplished by either Surgical Aortic Valve Replacement (SAVR) or by Transcatheter Aortic Valve Replacement (TAVR; Transcatheter Aortic Valve Implantation, TAVI).

While SAVR was the historical mainstay for treatment of severe, symptomatic AS, TAVR has taken off as the less invasive and increasingly popular alternative. The pool of TAVR-eligible patients has expanded rapidly over the last five years; in the United States, the Food and Drug Administration (FDA) first approved TAVR for severe AS patients who are at high surgical risk in 2015.[10-13] Studies then demonstrated that TAVR is non-inferior for intermediate-risk surgical patients as well,[14-17] and the FDA subsequently expanded eligibility to intermediate-risk patients in 2017. Finally, in 2019, the PARTNER 3

randomized trial demonstrated noninferiority of TAVR versus SAVR even for low-risk surgical patients with severe AS.[18] About three months later, TAVR was FDA-approved for use in low-risk surgical candidates.[19-21] With this dramatic increase in TAVR eligibility, the increasing global elderly population, and high prevalence of AS and severe AS, the number of TAVR procedures conducted annually is likely to continue increasing.

Conscious Sedation in TAVR

Earlier in the adoption of TAVR, the procedure was exclusively completed with patients under General Anesthesia (GA). However, as procedural knowledge has grown over the last decade, there has been a paradigm shift in anesthetic approach: Conscious Sedation (CS, also known as Moderate Sedation or Monitored Anesthesia Care[A]) has emerged as the viable alternative to GA. GA and CS represent different depths of sedation along the continuum of sedation.[22] GA is the deepest sedation possible, where patients are totally unresponsive to painful stimuli and require ventilation support. Conversely, CS consists of local anesthesia and parenteral medications that induce a state of depressed consciousness with anxiolysis and pain management. Unlike GA, CS does not require airway intervention, and patients are able to respond purposefully to tactile and verbal stimulation. CS generally results in less physiologic disturbance than GA, which typically leads to faster recovery times and decreased hospital length of stay.[23]

Indeed, the proportion of TAVR procedures completed under CS has been increasing. From 2013 to 2019, the percentage of transfemoral-access TAVR procedures performed under CS rather than GA went from 33% to 64%.[24] The increase in use of CS

[A] Per the American Society of Anesthesiologists, CS is termed "Monitored Anesthesia Care" (MAC) when administered by an anesthesiologist.

was likely bolstered by multiple observational and meta-analysis studies that demonstrated CS in TAVR results in equivalent procedure efficacy, shorter hospital stays, decreased ICU time, and decreased total cost of care compared to GA.[25-31] There has only been one prospective study to date that has compared TAVR outcomes after randomizing patients to GA or CS (SOLVE-TAVI), and this randomized study also found that CS resulted in equivalent outcomes, including mortality, stroke, myocardial infarction, paravalvular leak, and hospital and intensive care unit length of stay.[32] Additionally, the authors found that CS resulted in decreased use of inotropic agents compared to GA. Overall, anesthesia during TAVR has trended towards a minimalist approach with lighter sedation, and it is likely that CS will be an increasingly popular choice for anesthesia in TAVR.

Which Conscious Sedation medication regimen is optimal for TAVR?

The three most common sedatives for CS are propofol, midazolam, and dexmedetomidine, which are usually combined with opioids such as fentanyl and remifentanil for analgesia.[33] Each medication has benefits of use as well as potential adverse respiratory and hemodynamic effects:

- Propofol is a sedative-hypnotic that provides limited analgesia,[34] and it is the preferred agent for sedation in interventional procedures largely because of its rapid onset and short half-life, which allows it to be easily titrated and stopped for smooth recovery.[35] However, propofol also causes dose-dependent respiratory depression and cardiovascular depression that requires close monitoring,[22] and propofol is more likely to cause respiratory depression when co-administered with other sedatives and opioids.[33]

- Midazolam is a benzodiazepine with both anxiolytic and anterograde amnesia effects.[34] Like propofol, midazolam also does not offer analgesia and is usually paired with an opioid. Midazolam is also a dose-dependent respiratory depressant, and it has cardiovascular depressant effects, although these are usually minimal. Both the respiratory and cardiac depression effects increase when midazolam is co-administered with opioids or other sedatives.[33] Midazolam and other benzodiazepines can be reversed using flumazenil,[36] but propofol does not have a reversal agent.
- Dexmedetomidine is an alpha-2 adrenergic receptor agonist which, unlike propofol or midazolam, offers analgesia in addition to anxiolysis and sedation.[34] Dexmedetomidine causes minimal respiratory depression, and unlike propofol and midazolam, it does not synergize with other sedatives and opioids. However, it can induce both severe bradycardia and transient hypertension as a result of its sympatholytic effects.[33] There are no reversal agents currently available for human use.

Even though CS is widely used for TAVR, it remains unclear whether a certain CS medication regimen is more or less suited for TAVR patients. CS medications may not usually be expected to influence patients' clinical course beyond the procedure and immediately post-procedure, but there are several reasons why sedative choice may have a greater impact on clinical trajectory for TAVR patients. First, TAVR patients are overall elderly and therefore more sensitive to sedatives. Among low-surgical risk TAVR patients, the average age was 73,[18] and the average age for intermediate-risk patients was 82.[15] Geriatric patients are more sensitive to CS medication's intended effects and adverse side effects,[33] and they are more susceptible to over-sedation.[34] Consequently, it is recognized that elderly patients need lower doses of sedatives and closer monitoring of hemodynamic

response, and it may be more difficult to avoid sedative-associated complications in these patients.

Second, the conditions that render patients eligible for TAVR likely increases their sensitivity to adverse cardiovascular and respiratory effects of sedatives and makes it more difficult to avoid these complications. Patients must have severe aortic valve disease and a degree of symptomatic heart failure or measurable left ventricular dysfunction to be eligible for TAVR,[4] and these conditions result in a more friable hemodynamic system that is likely more vulnerable to CS medication-induced hemodynamic perturbations. Indeed, propofol, dexmedetomidine, and midazolam all decrease systemic vascular resistance, and this creates particular risk of hypotension in patients with AS; the stenotic valve is a fixed obstruction that causes decreased cardiac output, and decreased output drives myocardial hypoperfusion and decreased left ventricular contractility.[37] Furthermore, both propofol and dexmedetomidine are identified as agents that can exacerbate myocardial dysfunction and precipitate or worsen heart failure symptoms.[38] While completion of TAVR would address the valvular dysfunction and have an immediate effect on the patient's cardiovascular function, complications could still arise prior to valve replacement or occur despite the replacement due to advanced age or frailty.

Overall, increased risk of sedation-associated complications for these patients means there is increased risk that sedation choice could affect clinical course and longer-term outcomes for TAVR patients. If a patient experiences over-sedation intra-operatively, they may need intubation to address respiratory depression or pressor support and intensive care unit monitoring for persistent hemodynamic instability. Both outcomes after TAVR could cause longer hospital length of stay, and prolonged hospital stay (defined as hospital

stay greater than 72 hours) for TAVR patients is an independent predictor of 1-year all-cause mortality.[39] Ultimately, there is need to ascertain whether a given CS medication combination is associated with better or worse outcomes following TAVR, because this population has factors that increase risk of complications from sedation. If CS medications do affect outcomes even marginally, medication adjustments could lead to improvement of outcomes on an aggregate level due to the large number of TAVR operations conducted with CS annually.

To date, there are four studies that explore the effect of specific CS medications on patient outcomes after TAVR, and all four studies focus primarily on propofol versus dexmedetomidine. First, in 2016, Khalil et al. conducted a pilot study that randomized 50 patients to receive propofol (n=25) or dexmedetomidine (n=25) as CS agents for TAVR.[40] Authors found that both propofol and dexmedetomidine provided adequate sedation but that the dexmedetomidine patients had more intra-operative hemodynamic instability: patients treated with dexmedetomidine had significantly lower intra-operative heart rate and mean arterial blood pressure and required more phenylephrine boluses. However, authors found no differences between the group's post-operative complications, including hospital length of stay, ICU length of stay, mortality, renal failure, stroke, pulmonary edema, peripheral ischemia, local infection, ventricular arrhythmias, and myocardial ischemia.

Second, Mayr et al. compared propofol-opioid (n=150) versus dexmedetomidine only (n=157) in a retrospective analysis of TAVR CS regimens in 2017.[41] However, this study focused exclusively on outcomes relating to intra-operative hemodynamics and peri-procedural gas exchange, so the authors did not consider or compare post-operative

outcomes and complications. Mayr et al. found that the dexmedetomidine patients had significantly lower arterial partial pressure of carbon dioxide, lower frequency of hypercapnia, and lower need for norepinephrine than the propofol group. It was noted that conversion to GA occurred more frequently in the propofol group compared to the dexmedetomidine group, but the difference was not statistically significant.

Third, Chen et al. conducted a single institution, retrospective study in 2017 to compare propofol only (n=39) versus dexmedetomidine plus propofol (n=34).[42] The authors considered both post-operative outcomes and the effect of patient age on average dose. They found no significant difference between the groups, including in incidence of conversion to GA, total procedure time, incidence of post-operative delirium, hospital length of stay, and intensive care unit length of stay. Additionally, they found no association between patient age group and the doses of medications used.

Lastly, Kronfli et al. conducted a single institution, prospective observational study in 2020 to investigate outcomes and costs after TAVR with propofol (n=58) versus dexmedetomidine (n=103).[43] This was the only study to compare costs for these agents, and dexmedetomidine is typically a more costly agent than propofol. As was the case for the prior studies, the authors also found no significant difference in post-operative outcomes including in-hospital mortality, complication rate, need for pressors, and total cost of hospitalization. This was the largest study to date that considered outcomes (i.e., excluding Mayr et al.), but even this study cited small sample size as a key limitation.

While these four studies have helped get closer to identifying whether a given CS regimen is better for TAVR, the question remains open in several respects. First, these studies focused only on propofol versus either dexmedetomidine only or propofol plus

dexmedetomidine. However, there are other CS medication combinations that are currently in use in TAVR that are yet to be investigated for this procedure. For instance, no study has considered the effect of combination propofol plus midazolam versus propofol alone or midazolam alone in TAVR. For comparison, the combination of propofol plus midazolam has been studied for other procedures, including colonoscopy,[44-46] endoscopic procedures,[47-49] and pediatric sedation for MRI.[50] These studies found some differences between the comparators, with most finding that propofol plus midazolam resulted in deeper sedation and a longer recovery period. This could have implications for TAVR patient recovery and should be investigated further.

Second, while these studies found no significant difference in post-operative outcomes thus far, it is still possible that a difference exists but has not been detected. Of the studies that considered post-operative outcomes (Khalil et al., Chen et al., and Kronfli et al.), all three cited small sample size as a key limitation for the analyses. All three studies also specifically noted that complications of interest occurred at a very low rate and led to analyses that were underpowered. As a result, there is need to investigate CS medications using larger sample sizes to identify any differences that may previously have been obscured by small samples.

STATEMENT OF PURPOSE

We set out to investigate whether a given CS regimen of interest is associated with better or worse post-TAVR outcomes, with primary focus on total hospital length of stay (LOS), mortality, and need for post-operative permanent pacemaker. Incidence of post-operative permanent pacemaker (PPM) is also a key outcome of interest, because while other post-TAVR complications have decreased with time, incidence of post-operative PPM has paradoxically increased[51] and could be affected by CS choice, especially propofol[52] or dexmedetomidine.[53]

Medication Groups and Hypotheses

First, we set out to test whether CS with either propofol or propofol plus midazolam could lead to worse outcomes after TAVR. Both propofol and benzodiazepines cause respiratory depression, especially if they are co-administered,[33,54] and respiratory depression is the most common complication of CS.[33] Indeed, in a 2006 analysis of claims data, over half of the patients who experienced respiratory depression and associated complications after CS had received propofol with or without a benzodiazepine.[55] Furthermore, geriatric patients are more susceptible to the adverse effects of propofol and midazolam.[33] As a result, these CS medications may lead to increased risk of over sedation, which could potentially lengthen hospital stay and lead to increased related post-procedural complications such as conversion to GA or in-hospital death.

There is also evidence that propofol may provide less adequate post-operative pain amelioration and may lead to increased need for post-operative pain management One study comparing propofol to dexmedetomidine for CS in minor hysteroscopic

surgery found that propofol resulted in worse intraoperative analgesia and higher pain scores post-operatively.[56] Another randomized trial studying the effect of propofol versus dexmedetomidine following total knee arthroplasty with spinal anesthesia and CS found that propofol patients required increased post-operative opioids.[57] Post-operative pain and increased opioids both increase risk of delirium,[58] which is of concern for this majority geriatric patient population and could prolong hospital stay. Overall, investigation of the effect of propofol and propofol plus midazolam on TAVR outcomes is warranted and will be explored via the following analyses:

- **Hypothesis A:** Use of propofol for CS in TAVR, regardless of other medications used, is associated with worse outcomes (longer LOS, increased hazard of mortality, or increased need for post-operative PPM). Analysis A will compare outcomes after CS with Propofol versus CS with No propofol.
- **Hypothesis B:** CS in TAVR with propofol plus midazolam will be associated with worse outcomes than CS with propofol only. Analysis B will be a comparison of outcomes after Propofol plus midazolam versus Propofol only.

Second, we set out to investigate whether dexmedetomidine use is associated with better outcomes after TAVR. While both Khalil et al. and Mayr et al. found that dexmedetomidine resulted in lower intra-operative blood pressures, neither study demonstrated worse dexmedetomidine outcomes. In fact, there are several reasons why dexmedetomidine may be potentially beneficial for post-operative outcomes. First, a 2019 meta-analysis that found dexmedetomidine may reduce incidence of delirium after cardiac surgery,[59] and dexmedetomidine has been associated with reduced post-operative pain

compared to propofol[56,60] and overall reduced risk of acute kidney injury.[61,62] Use of dexmedetomidine is also associated with reduced risk of intra-operative respiratory depression compared to CS with benzodiazepines or propofol with opioids.[63] Indeed, in a study of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), patients treated with dexmedetomidine plus ketamine rather than propofol plus opioids experienced significantly fewer adverse sedation-related events.[64] Additionally, there is some evidence that dexmedetomidine could reduce risk of arrythmias, but this evidence is mixed.[53,65,66] Overall, dexmedetomidine could potentially benefit the TAVR patient population due to its effects on these common post-procedural complications and will be investigated by the following analysis:

- **Hypothesis C:** Use of dexmedetomidine in CS for TAVR, regardless of other medications, will be associated with improved outcomes. Analysis C will compare outcomes after CS with Dexmedetomidine versus CS with No Dexmedetomidine.

METHODS

Author D. Somlo wrote, submitted, achieved approval, and re-submitted the protocol for re-approval as necessary. This study received approval from the Institutional Review Board (Protocol #2000021153), and individual patient consent was waived, as this was a retrospective analysis.

Ethics Statement

There were no ethical concerns related to this study, and the entirety of the study was conducted in accordance with the approved protocol.

Patients

The study population included all patients who underwent TAVR for the treatment of severe Aortic Stenosis with plan for conscious sedation at Yale New Haven Hospital (New Haven, Connecticut) between September 2014 and December 2017. All patients were evaluated by the Structural Heart Disease Team and were determined to be candidates for TAVR rather than Surgical Aortic Valve Replacement (SAVR) based on standardized assessment.

Data Collection

To identify patients in this cohort, D. Somlo requested patient medical record numbers from the institutional Joint Data Analytics Team. Following review board approval of the protocol, the Joint Data Analytics Team provided the record numbers and accompanying data on patient demographics, comorbidities, procedure characteristics, and outcomes

recorded for the Society of Thoracic Surgery (STS)/American College of Cardiology TVT Registry. D. Somlo and Usman Bin Mahmood, MBBS, then completed manual chart review using the healthcare system's electronic medical record system, EPIC, to verify and update all data using definitions from the STS/ACC TVT Registry v2.0 Coder's Data Dictionary. D. Somlo completed further chart review to clarify the cause of intraprocedural conversion to general anesthesia, intraprocedural conversion to surgery, or hospital length of stay greater than 3 days.

Mortality Data Collection

D. Somlo requested and obtained patient mortality data up to February 1, 2020 from both chart review and from the Connecticut Department of Public Health. D. Somlo requested records from the Connecticut Department of Public Health for January 2014 and December 2018. The state records were checked against each patient's corresponding medical record in EPIC to verify the mortality outcomes and dates. If a death was recorded in the state records but not in EPIC, the state record was used. Conversely, if a patient was recorded as deceased in EPIC but not in the state data, the EPIC data was used. 14 of the 60 deceased patients (23%) were not recorded in the state records, because they were either not Connecticut residents or passed after December 2018.

Risk Score Calculation

Of the 277 patients included in the analyses, 8 patients did not have STS Risk of Mortality Scores in their charts. For these patients, D. Somlo calculated STS Risk of Mortality using the online STS Calculator (version 2.9) by inputting the following variables obtained

through chart review: age, sex, height, weight, current dialysis, hypertension, immunocompromised status, prior peripheral arterial disease, prior cerebrovascular disease or stroke, diabetes, chronic lung disease, smoking status, use of home oxygen, prior Coronary Artery Bypass Grafting (CABG), prior Percutaneous Coronary Intervention (PCI), prior aortic valve replacement, prior Myocardial Infarction, New York Heart Association (NYHA) heart failure score from the prior 2 weeks, Coronary Artery Disease (CAD) presenting symptoms, prior cardiogenic shock, pre-existing atrial fibrillation or atrial flutter, pre-existing conduction defect, number of diseased coronary vessels, previous permanent pacemaker, previous implantable cardioverter-defibrillator, status of TAVR (elective, urgent, emergent), and prior cardiac arrest.

Dose calculations

To normalize medication doses for comparison, D. Somlo used the same approach as Chen et al.[42] First, chart review was completed to obtain total quantities of each medication administered intraoperatively. Each medication quantity was then divided by each patient's mass (kg) and length of procedure (hours) to obtain dose in units of mcg/kg/hour or mg/kg/hour.

Statistical Analysis and Figures

All statistical testing for this study was completed by D. Somlo, with assistance and support from Makoto Mori, MD. Summary statistics of baseline patient characteristics, procedural characteristics, and procedure outcomes and the multivariable linear and logistic regression analysis were completed using GraphPad Prism version 9.0.0 (GraphPad Software, San

Diego, CA, United States). Cox proportional hazard analyses were completed in Stata 15.0 (StataCorp, College Station, TX, United States). An alpha of 0.05 was used as the cut-off for significance, and all comparisons were two-sided. Descriptive statistics for continuous variables were reported as mean with standard deviation, and categorical variables were reported as count (percentage). For statistical comparison tests, continuous variables were analyzed with ANOVA, and categorical variables were analyzed via Chi-square tests. For comparisons of continuous variable distributions (cases over time, drug dose comparisons), Kolmogorov-Smirnov tests were conducted. An outlier for length of stay was identified using outlier analysis in GraphPad Prism (shown in Fig. 4). The outlier was only excluded from regression analysis of hospital length of stay. All figures were generated by D. Somlo. All figures were created using GraphPad Prism, with the exception of the Sankey diagram (Fig. 1) generated using free online software, SankeyMATIC (http://sankeymatic.com/build/).

RESULTS

Patient CS medication groups are shown in Fig. 1. A total of 706 TAVR patients were identified. 61% of patients (n=429) were treated with GA and were excluded. At the study institution, CS is conducted by anesthesiology trainees and attending physicians for TAVR. Per the American Society of Anesthesiologists, CS administered by an anesthesiologist is referred to as "Monitored Anesthesia Care" (MAC), so CS will be referred to as "MAC" for this study.

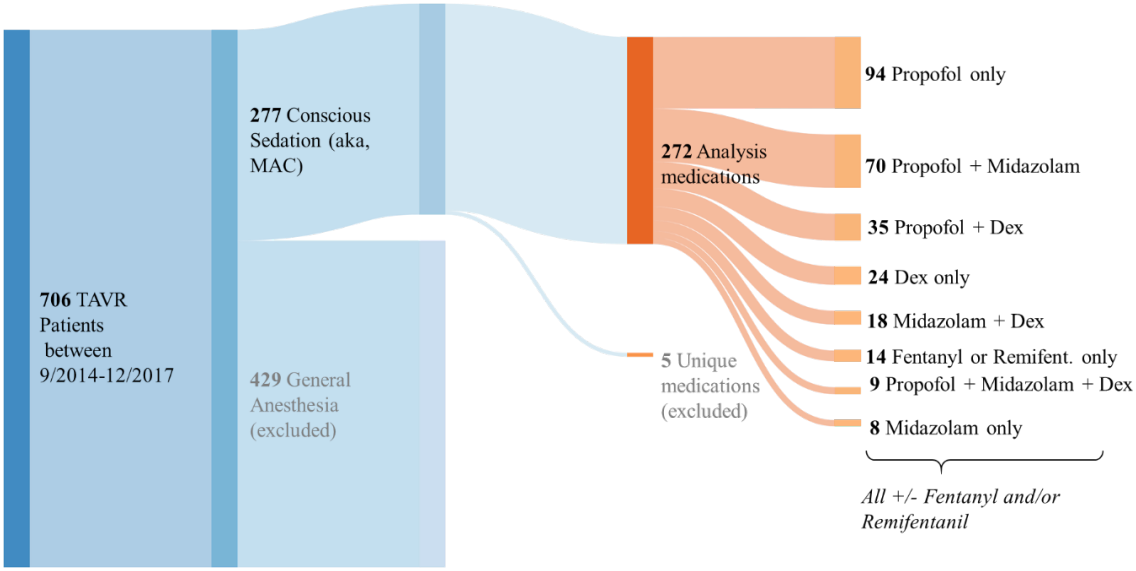

Figure 1: Sankey Diagram of patient exclusion and grouping. 272 of the 277 Conscious Sedation patients were included in further analysis. Analyses A, B, and C examine different combinations of the identified medication subgroups at the far right. MAC, Monitored Anesthesia Care; Dex, Dexmedetomidine; Remifent., Remifentanil.

39% of TAVR cases (n=277) were completed under MAC. MAC patients were treated with three main sedatives – propofol, midazolam, or dexmedetomidine – as well as opioids (fentanyl and remifentanil). 5 of the 277 MAC patients were treated with unique medications: hydromorphone (n=3), morphine (n=1), or ketamine (n=1). These 5 patients were excluded from further analysis. Additionally, it was noted during chart review that

many patients received lidocaine for local anesthesia, but lidocaine use and doses were not considered. Three separate analyses were conducted from this pool of MAC patients to assess characteristics and outcomes associated with different medication groups: *Propofol versus No Propofol* (Analysis A), *Propofol plus midazolam versus Propofol only* (Analysis B), and *Dexmedetomidine versus No Dexmedetomidine* (Analysis C).

Analysis A: Propofol versus No Propofol

272 CS patients were grouped based on whether or not they received propofol as part of their MAC treatment. n=5 patients received a dose of propofol that was likely subtherapeutic (<20mg total) and were excluded from both groups. The remaining 267 patients were divided into the *Propofol group* (n=203) and the *No Propofol group* (n=64). Patient characteristics are reported in Table A1. The groups only differed significantly in pre-operative permanent pacemaker (PPM), where the Propofol group had a lower rate of pre-operative PPM (10.8% versus 23.4%; p = 0.021). To detect any era effect, the distribution of cases by procedure date was examined. There was no significant difference in the distribution of cases over time between the groups (Kolmogorov-Smirnov test, p = 0.19, Fig. 2).

Table A1 - Propofol vs. No Propofol
Baseline Patient Characteristics

	Propofol group (n=203)	**No Propofol group (n=64)**	**P Value**
Age (years)	82.5 ± 8.1	83.0 ± 8.8	0.68
Male sex	111 (54.7%)	38 (59.4%)	0.56
BMI (kg/m^2)	28.0 ± 5.6	28.9 ± 6.3	0.27
STS Risk of Mortality Score	6.2 ± 3.9	6.6 ± 5.0	0.56
Hypertension	175 (86.2%)	54 (84.3%)	0.69
Diabetes	70 (34.5%)	26 (40.6%)	0.38
Currently on dialysis	5 (2.5%)	1 (1.6%)	>0.99
Peripheral arterial disease	38 (18.7%)	10 (15.6%)	0.71
Cerebrovascular disease/TIA	19 (9.4%)	5 (7.8%)	0.81

Prior Stroke	17 (8.4%)	5 (7.8%)	>0.99
Immunocompromised	28 (13.8%)	3 (9.7%)	0.07
Chronic lung disease	37 (18.2%)	8 (12.5%)	0.34
Current or former smoker	126 (62.1%)	36 (56.3%)	0.46
Home oxygen	12 (5.9%)	1 (1.6%)	0.20
Atrial fibrillation	71 (35.0%)	23 (35.9%)	0.88
Atrial flutter	8 (3.9%)	5 (7.8%)	0.31
Conduction defect	55 (27.1%)	20 (31.3%)	0.53
Permanent pacemaker	22 (10.8%)	15 (23.4%)	**0.02 ***
Diseased coronary vessels - none	90 (44.3%)	25 (39.1%)	0.17
Diseased coronary vessels - 1	49 (24.1%)	14 (21.9%)	
Diseased coronary vessels - 2	37 (18.2%)	9 (14.1%)	
Diseased coronary vessels - 3	27 (13.3%)	16 (25%)	
Diseased proximal LAD	51 (25.1%)	23 (35.9%)	0.11
Diseased left main coronary artery	16 (7.9%)	11 (17.2%)	0.054
Prior myocardial infarction	55 (27.1%)	13 (20.3%)	0.33
Prior PCI	70 (34.5%)	23 (35.9%)	0.88
Prior coronary artery bypass	46 (22.7%)	18 (29.7%)	0.32
NYHA Class II	29 (14.3%)	14 (21.9%)	0.31
NYHA Class III	148 (72.9%)	44 (68.8%)	
NYHA Class IV	26 (12.8%)	6 (9.4%)	
Prior aortic valve replacement	18 (8.9%)	3 (4.7%)	0.42
Elective procedure	188 (92.6%)	60 (93.75%)	>0.99
Urgent procedure	15 (7.4%)	4 (6.25%)	
No anginal symptoms	172 (84.7%)	54 (84.4%)	0.99
Angina, NSTEMI, STEMI	10 (4.9%)	3 (4.7%)	
Likely non-ischemic symptoms	21 (10.3%)	7 (10.9%)	
Pre-procedure hemoglobin (g/dL)	11.9 ± 1.7	11.9 ± 2.1	0.90
Pre-procedure creatinine (mg/dL)	1.2 ± 0.9	1.1 ± 0.3	0.13
Pre-procedure platelets (per µL)	210k ± 93k	209k ± 78k	0.90

TAVR, Transcatheter Aortic Valve Replacement; CS, Conscious Sedation; BMI, Body Mass Index; STS, Society of Thoracic Surgeons; TIA, Transient Ischemic Attack; LAD, Left Anterior Descending coronary artery; PCI, Percutaneous Coronary Intervention; NYHA Class, New York Heart Association classification of heart failure; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

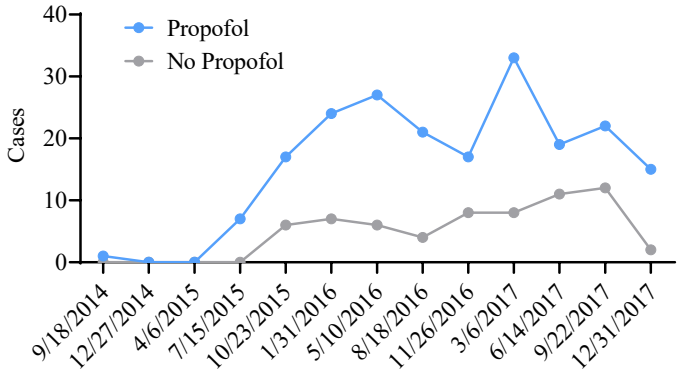

Figure 2: TAVR Cases over time for Propofol versus No Propofol. Absolute case numbers varied over time in both groups, but the distributions of cases were not significantly different (Kolmogorov-Smirnov test, p = 0.19).

Procedural characteristics are presented in Table A2. All TAVR procedures were completed from a femoral entry site, via either percutaneous or cut-down access. 2% of procedures in the Propofol group were completed with cutdown access, and none of procedures in the No Propofol group were completed with cutdown (p = 0.58, Table A2). A significantly lower percentage of Propofol group was treated with dexmedetomidine (21.7% versus 65.6%, p <0.0001) and with remifentanil (13.3% versus 40.6%, p <0.0001, Table A2). To investigate whether medication doses also differed between the groups, doses were calculated according to the method used by Chen et al.[42] Doses of each medication were plotted by group (Figure 3)[B]. Only remifentanil doses differed significantly between the groups, where the Propofol group received lower doses of remifentanil (mean dose 1.17 mcg/kg/hr versus 2.34 mcg/kg/hr, p = 0.0024).

Table A2 - Propofol vs. No Propofol
Summary Statistics of Procedural Characteristics

	Propofol (n=203)	No Propofol (n=64)	P Value
Valve-in-valve procedure	12 (5.9%)	2 (3.1%)	0.53
Percutaneous Access	199 (98%)	64 (100%)	0.58
Cutdown Access	4 (2%)	0	
Treated with propofol	203 (100%)	0	-
Propofol dose (mg/kg/hr)	1.03 ± 0.7	-	-
Treated with midazolam	79 (38.9%)	26 (40.6%)	0.88
Midazolam dose (mcg/kg/hr)	7.0 ± 3.9	6.8 ± 3.6	0.65
Treated with dexmedetomidine	42 (20.7%)	42 (65.6%)	**<0.0001 ***
Dexmedetomidine dose (mcg/kg/hr)	0.38 ± 0.2	0.41 ± 0.2	0.065
Treated with fentanyl	171 (84.2%)	54 (84.4%)	>0.99
Fentanyl dose (mcg/kg/hr)	0.42 ± 0.3	0.42 ± 0.3	0.56
Treated with remifentanil	27 (13.3%)	26 (40.6%)	**<0.0001 ***
Remifentanil dose (mcg/kg/hr)	1.2 ± 1.0	2.3 ± 1.5	**0.002 ***

[B] Because the doses were normalized to anesthesia time rather than total medication infusion time, the resulting doses are lower than what is expected from dosing guidelines for each medication.

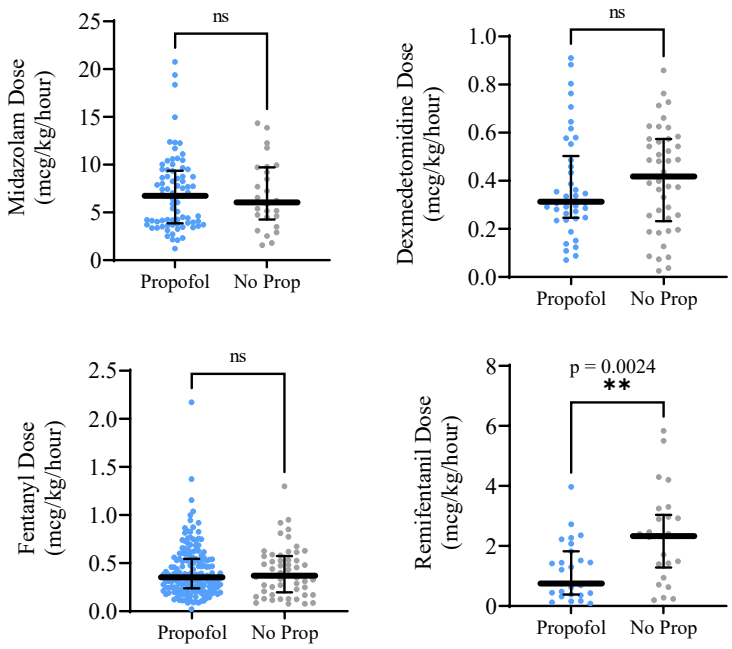

Figure 3: Comparison of medication doses between the Propofol versus No Propofol group. The Kolmogorov-Smirnov test was used to compare doses. ns, Not signifcant.

Analysis A: Unadjusted outcomes

Unadjusted outcomes are shown in Table A3a. Total anesthesia time did not differ significantly between the groups (202 versus 195 minutes, p = 0.27), and no procedures were aborted. There were 2 conversions to GA, with 1 conversion in the Propofol group (0.5%) and 1 in the No Propofol group (1.6%, p = 0.42). The patient who was converted to GA in the Propofol group was an 84-year-old female who became hypotensive and bradycardic during the procedure, requiring epinephrine and a brief period of cardiopulmonary resuscitation. She was converted to GA when she was intubated for stabilization. For the case in the No Propofol group, a 91-year-old male was noted to have hypercarbia and converted to GA for intubation. No procedures were converted to surgical valve replacement. There was no significant difference in in-hospital mortality (0.5%

versus 1.6%, p = 0.42) or in discharge location (81.3% versus 79.7% discharged to home or nursing home, p = 0.85).

Table A3a - Propofol vs. No Propofol
Unadjusted, Descriptive Statistics of Peri- and Postoperative Outcomes

	Propofol (n=203)	No Propofol (n=64)	P Value
Total anesthesia time (minutes)	202 ± 45	195 ± 33	0.27
Conversion to general anesthesia	1 (0.5%)	1 (1.6%)	0.42
Conversion to surgical replacement	0	0	-
Procedure aborted	0	0	-
Deceased in-hospital	2 (1.0%)	1 (1.6%)	0.42
Discharged to hospice	1 (0.5%)	0	>0.99
Home or nursing home	165 (81.3%)	51 (79.7%)	>0.99
Rehab/extended care/ transitional care unit	35 (17.2%)	12 (18.8%)	

Specific attention was paid to patients with prolonged LOS after TAVR (≥ 4 days), which is associated with all-cause mortality and worse outcomes at 1-year post-TAVR.[39] Chart review was conducted for patients with LOS ≥ 4 days, and unadjusted results are shown in Table A3b. There was no significant difference in the percentage of patients who had prolonged LOS between the Propofol versus No Propofol groups, and there were no significant associations between medication group and incidence of specific causes of prolonged hospitalization.

Table A3b - Propofol vs. No Propofol (Patients with LOS ≥ 4 days)
Unadjusted, Descriptive Statistics of Postoperative Complications

	Propofol (n=43)	No Propofol (n=13)	P value
Incidence of LOS ≥ 4 days	43 (21.2%)	13 (20.3%)	>0.99
Fluid overload	13 (30.2%)	6 (46.2%)	0.33
Hypotension	12 (27.9%)	3 (23.1%)	>0.99
Heart block	12 (27.9%)	5 (38.5%)	0.50
PPM Placement	11 (25.6%)	5 (38.5%)	0.49
Bleeding	9 (20.9%)	3 (23.1%)	>0.99
Elevated creatinine	8 (18.6%)	2 (15.4%)	>0.99
Infection	8 (18.6%)	2 (15.4%)	>0.99
New arrhythmia	4 (9.3%)	1 (7.7%)	>0.99
Delirium	4 (9.3%)	1 (7.7%)	>0.99
Stroke	3 (7.0%)	0	>0.99

Hypertension	3 (7.0%)	0	>0.99
TIA	2 (4.7%)	0	>0.99
Urinary retention	2 (4.7%)	1 (7.7%)	0.55
Diarrhea	1 (2.3%)	1 (7.7%)	0.41
Pseudogout	1 (2.3%)	0	>0.99
Limb ischemia	1 (2.3%)	0	>0.99

Analysis A: Adjusted Outcomes

Linear regression analysis was conducted to adjust for the significantly different baseline characteristics when assessing for association between the Propofol group and continuous variable outcomes. Results are shown in Table A4. One patient in the Propofol group had a LOS of 32 days (shown in Fig. 4) and was excluded as an outlier from the LOS analysis. When controlling for pre-operative PPM, treatment with dexmedetomidine, and remifentanil dose, the Propofol group was not significantly associated with a change in hospital LOS (Coefficient 0.5 days, 95%CI: [-0.2, 1.2], p = 0.15), change in creatinine from pre- to post-procedure (Coefficient 0.04 mg/dL, 95%CI: [-0.1, 0.2], p = 0.60), change in hemoglobin pre- to post-procedure (Coefficient -0.4 g/dL, 95%CI: [-0.9, 0.06], p = 0.084), or creatinine at discharge (Coefficient 0.24 mg/dL, 95%CI: [-0.03, 0.5], p = 0.09).

Table A4 - Propofol vs. No Propofol
Linear Regression Analyses

Regression Outcome	Variable	Coefficient	95% CI	P Value
Hospital length of stay (days) (one outlier excluded from Propofol group)	*Propofol (versus No Propofol)*	*0.498*	*-0.175, 1.170*	*0.15*
	Pre-op Permanent Pacemaker	-0.104	-0.788, 0.580	0.76
	Treated with Dexmedetomidine	0.464	-0.102, 1.030	0.11
	Remifentanil Dose, mcg/kg/hr	-0.079	-0.359, 0.202	0.58
Change in Creatinine, pre to post-procedure (mg/dL)	*Propofol*	*0.038*	*-0.104, 0.180*	*0.60*
	Pre-op Permanent Pacemaker	-0.041	-0.186, 0.104	0.57
	Treated with Dexmedetomidine	0.046	-0.074, 0.166	0.45
	Remifentanil Dose, mcg/kg/hr	-0.028	-0.087, 0.031	0.35
Change in Hemoglobin, pre to post-procedure (g/dL)	*Propofol*	*-0.415*	*-0.887, 0.057*	*0.084*
	Pre-op Permanent Pacemaker	-0.030	-0.510, 0.450	0.90
	Treated with Dexmedetomidine	-0.211	-0.608, 0.186	0.30
	Remifentanil Dose, mcg/kg/hr	-0.186	-0.383, 0.011	0.064

Creatinine at discharge (mg/dL)	*Propofol*	*0.239*	*-0.035, 0.513*	*0.09*
	Pre-op Permanent Pacemaker	-0.008	-0.286, 0.270	0.95
	Treated with Dexmedetomidine	0.150	-0.080, 0.379	0.20
	Remifentanil Dose, mcg/kg/hr	0.016	-0.099, 0.131	0.78

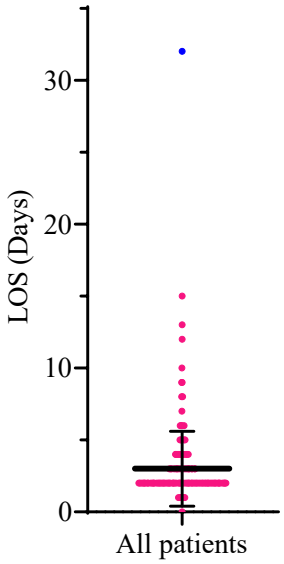

Figure 4: Comparison of length of stay for all MAC patients. All MAC cases (n=272) were plotted by total LOS. One outlier was identified (blue dot, LOS = 32 days). This outlier was a patient who was treated with propofol and midazolam, and this patient was excluded from regression analysis for LOS in Analysis A, B, and C. Excluding the outlier: mean LOS, 2.9 days; Standard Deviation, 1.9 days. Median LOS, 2.0 days; Interquartile Range 2.0-3.0 days.

Logistic regression analysis was used to assess the association of the Propofol group with binary outcomes while adjusting for different baseline characteristics. Regression results are shown in Table A5. Inclusion in the Propofol group was not significantly associated with incidence of post-operative PPM (Odds Ratio 3.4, 95%CI: [0.3, 91.6], p = 0.36, Table A5) or need for red blood cell (RBC) transfusion post-operatively (OR 1.1, 95%CI: [0.3, 5.0], p = 0.89). For the analysis of post-operative PPM, 37 patients were excluded, because they had pre-operative PPMs (Propofol group n=22, 10.8% versus n=15, 23.4%, Table A1). Lastly, Cox proportional hazard analysis was used to test for any association of MAC medication group with mortality while adjusting for baseline differences. Results are shown in Table A6. There was no significant association

between the Propofol group and mortality compared to the No Propofol group (Hazard Ratio 1.1, 95%CI: [0.5, 2.3], p = 0.81, Table A6).

Table A5 - Propofol vs. No Propofol
Logistic Regression Analyses

Regression Outcome	Variable	Odds Ratio	95% CI	P Value
Post-operative PPM, excluding pre-existing PPM (n= 230)	*Propofol (versus No Propofol)*	*0.733*	*0.242, 2.312*	*0.58*
	Treated with Dexmedetomidine	0.706	0.260, 1.729	0.47
	Remifentanil Dose, mcg/kg/hr	0.674	0.328, 1.115	0.19
RBC transfusion	*Propofol*	*1.105*	*0.286, 4.991*	*0.89*
	Pre-op Permanent Pacemaker	1.135	0.249, 3.749	0.85
	Treated with Dexmedetomidine	0.731	0.203, 2.213	0.60
	Remifentanil Dose, mcg/kg/hr	0.966	0.470, 1.617	0.91

Table A6 - Propofol vs. No Propofol
Cox Proportional Hazard Model Outcomes

Regression Outcome	Variable	Hazard Ratio	95% CI	P Value
Mortality	*Propofol (versus No Propofol)*	*1.095*	*0.527, 2.276*	*0.81*
	Pre-op Permanent Pacemaker	0.579	0.243, 1.378	0.22
	Treated with Dexmedetomidine	1.382	0.771, 2.475	0.28
	Remifentanil Dose, mcg/kg/hr	0.867	0.596, 1.262	0.46

Analysis B: Propofol plus midazolam versus Propofol only

The *Propofol plus midazolam group* (n=70) and *Propofol only group* (n=94) were isolated for the second analysis. Patient characteristics are reported in Table B1. There were several characteristics that were significantly different between groups: the Propofol plus midazolam group was younger (78.8 ± 8.3 years versus 85.9 ± 6.0 years; p < 0.0001), had higher body mass index (BMI, 30.0 ± 5.7 versus 27.1 ± 5.1; p = 0.0009), had a lower mean STS Risk of Mortality Score (5.3 ± 3.7 versus 6.4 ± 5.3; p = 0.039), lower prevalence of atrial fibrillation (25.7% versus 48.9%; p = 0.004), and higher prevalence of previous myocardial infarction (35.7% versus 17.0%; p = 0.01). There was no significant difference in the distribution of cases over time (p = 0.27, Fig. 5).

Table B1 - Propofol plus midazolam vs. Propofol only
Baseline Patient Characteristics

	Propofol plus midazolam (n=70)	Propofol only (n=94)	P Value
Age (years)	78.8 ± 8.3	85.9 ± 6.0	**<0.0001***
Male sex	41 (44.1%)	52 (55.9%)	0.75
BMI (kg/m^2)	30.0 ± 5.7	27.1 ± 5.1	**0.0009 ***
STS Risk of Mortality Score	5.3 ± 3.7	6.4 ± 5.3	**0.04 ***
Hypertension	62 (88.6%)	78 (83.0%)	0.38
Diabetes	29 (41.4%)	25 (26.6%)	0.064
Currently on dialysis	0	2 (2.1%)	0.51
Peripheral arterial disease	9 (12.9%)	15 (16.0%)	0.66
Cerebrovascular disease/TIA	8 (11.4%)	7 (7.5%)	0.42
Prior Stroke	5 (7.1%)	5 (5.3%)	0.75
Immunocompromised	10 (14.3%)	11 (11.7%)	0.64
Chronic lung disease	11 (15.7%)	18 (19.2%)	0.68
Current or former smoker	46 (65.7%)	55 (58.5%)	0.42
Home oxygen	4 (5.7%)	3 (3.2%)	0.46
Atrial fibrillation	18 (25.7%)	46 (48.9%)	**0.004 ***
Atrial flutter	4 (5.7%)	3 (3.2%)	0.46
Conduction defect	14 (20.0%)	30 (31.2%)	0.11
Permanent pacemaker	4 (5.7%)	14 (14.9%)	0.08
Diseased coronary vessels - none	32 (45.7%)	41 (43.6%)	0.70
Diseased coronary vessels - 1	19 (27.1%)	21 (22.3%)	
Diseased coronary vessels - 2	9 (12.9%)	18 (19.1%)	
Diseased coronary vessels - 3	10 (14.3%)	14 (14.9%)	
Diseased proximal LAD	19 (27.1%)	26 (27.6%)	>0.99
Diseased left main coronary artery	5 (7.1%)	7 (7.5%)	>0.99
Prior myocardial infarction	25 (35.7%)	16 (17.0%)	**0.01 ***
Prior PCI	22 (31.4%)	36 (38.3%)	0.41
Prior coronary artery bypass	18 (25.7%)	17 (18.1%)	0.25
NYHA Class II	15 (21.4%)	10 (10.6%)	0.16
NYHA Class III	47 (67.1%)	71 (75.5%)	
NYHA Class IV	8 (11.4%)	13 (13.8%)	
Prior aortic valve replacement	6 (8.6%)	8 (8.5%)	>0.99
Elective procedure	64 (91.4%)	88 (93.6%)	0.76
Urgent procedure	6 (8.6%)	6 (6.4%)	
No anginal symptoms	58 (82.9%)	80 (85.1%)	0.72
Angina, NSTEMI, STEMI	7 (10%)	10 (10.6%)	
Likely non-ischemic symptoms	5 (7.1%)	4 (4.3%)	
Pre-procedure hemoglobin (g/dL)	12.1 ± 1.6	11.7 ± 1.8	0.17
Pre-procedure creatinine (mg/dL)	1.2 ± 0.6	1.2 ± 0.8	0.99
Pre-procedure platelets (per µL)	205k ± 97k	209k ± 88k	0.76

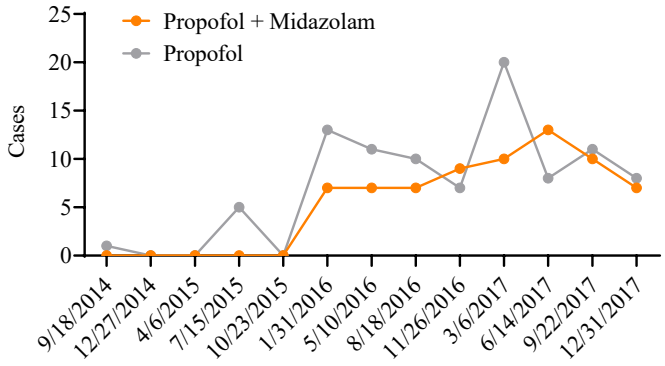

Figure 5: TAVR Cases over time for Propofol plus Midazolam versus Propofol. The distributions of cases over time were not significantly different (Kolmogorov-Smirnov test, p = 0.27).

Procedural characteristics are presented in Table B2. Cutdown procedures were only conducted in the Propofol group (n=2, 2.1%, p = 0.51). A significantly lower percentage of patients in the Propofol plus midazolam group were treated with remifentanil (8.6% versus 22.3%; p = 0.02, Table B2), and the Propofol plus midazolam group was treated with a significantly higher dose of fentanyl (mean dose 0.52 mcg/kg/hr versus 0.35 mcg/kg/hr, p = 0.0002, Fig. 6). All other medications and doses were not significantly different.

Table B2 – Propofol plus midazolam vs. Propofol
Summary Statistics of Procedural Characteristics

	Propofol plus midazolam (n=70)	**Propofol (n=94)**	**P Value**
Valve-in-valve procedure	3 (4.3%)	6 (6.4%)	0.73
Percutaneous Access	70 (100%)	92 (97.9%)	0.51
Cutdown Access	0	2 (2.1%)	
Treated with propofol	70 (100%)	94 (100%)	-
Propofol dose (mg/kg/hr)	1.0 ± 0.7	1.1 ± 0.7	0.18
Treated with midazolam	70 (100%)	0	-
Midazolam dose (mcg/kg/hr)	7.1 ± 4.0	-	-
Treated with fentanyl	63 (90%)	78 (83.0%)	0.26
Fentanyl dose (mcg/kg/hr)	0.52 ± 0.2	0.35 ± 0.2	**0.0002** *
Treated with remifentanil	6 (8.6%)	21 (22.3%)	**0.02** *
Remifentanil dose (mcg/kg/hr)	1.2 ± 1.4	1.2 ± 0.9	0.84

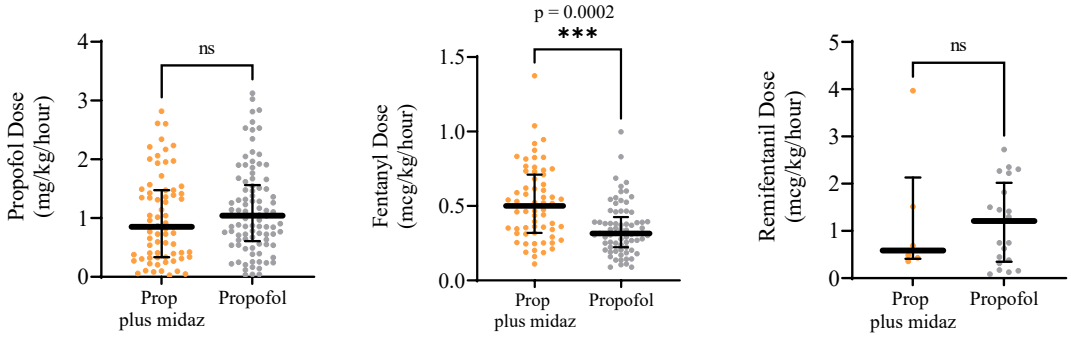

Figure 6: Comparison of medication doses between Propofol plus Midazolam versus Propofol only. The Kolmogorov-Smirnov test was used to compare doses. ns, not significant; Prop, Propofol.

Analysis B: Unadjusted outcomes

Unadjusted procedure outcomes are shown in Table B3a. Total anesthesia time was not significantly different between the groups. There was 1 conversion to GA in the Midazolam plus Propofol group (1.4%), and there was no significant difference in in-hospital mortality (1.4% versus 1.1%, $p > 0.99$). There was also no difference in discharge locations between the groups (82.9% versus 79.8% discharged to home or nursing home, $p = 0.53$).

Table B3a – Propofol plus midazolam vs. Propofol only
Unadjusted, Descriptive Statistics of Peri- and Postoperative Outcomes

	Propofol plus midazolam (n=70)	Propofol only (n=94)	P Value
Total anesthesia time (minutes)	197 ± 42	200 ± 41	0.71
Conversion to general anesthesia	1 (1.4%)	0	0.43
Conversion to surgical replacement	0	0	-
Procedure aborted	0	0	-
Deceased in-hospital	1 (1.4%)	1 (1.1%)	>0.99
Discharged to hospice	1 (1.4%)	0	0.43
Discharged to home or nursing home	58 (82.9%)	75 (79.8%)	>0.99
Discharged to rehab/extended care/transitional care unit	10 (14.3%)	12 (12.8%)	

Analysis of patients with LOS ≥ 4 days is shown in Table B3b. The Propofol plus midazolam group had a lower percent of patients with LOS ≥ 4 days, but the difference was not significant (12.9% versus 24.5%, p = 0.075, Table B3b). Since this analysis was unadjusted, the association between the medication groups and prolonged LOS was also tested using logistic regression to adjust for different baseline variables (Table B5). In the adjusted analysis, the association remained non-significant (Odds Ratio 0.85, 95%CI: [0.3, 2.4], p = 0.78). Additionally, the Propofol plus midazolam group had a higher percentage of patients who experienced hypotension as part of the cause of their prolonged length of stay (55.5% versus 17.4%, p = 0.075, Table B3b). This association was also tested with adjustment (Table B5), and the association remained non-significant (Odds Ratio 5.8, 95%CI: [0.6, 81.6], p = 0.14, Table B5).

Table B3b – Propofol plus midazolam vs. Propofol only (Patients with LOS ≥ 4 days)
Unadjusted, Descriptive Statistics of Postoperative Complications

	Propofol plus midazolam (n=9)	Propofol only (n=23)	P Value
Incidence of LOS ≥ 4 days	9 (12.9%)	23 (24.5%)	0.075
Hypotension	5 (55.5%)	4 (17.4%)	0.075
Fluid overload	3 (33.3%)	5 (21.8%)	0.65
Elevated creatinine	3 (33.3%)	3 (13.0%)	0.31
Heart block	3 (33.3%)	6 (26.1%)	0.69
PPM Placement	3 (33.3%)	5 (21.8%)	0.65
Infection	2 (22.2%)	4 (17.4%)	>0.99
Stroke	2 (22.2%)	1 (4.3%)	0.18
Bleeding	1 (11.1%)	6 (26.1%)	0.64
Hypertension	1 (11.1%)	2 (8.7%)	>0.99
Delirium	1 (11.1%)	1 (4.3%)	0.49
Limb ischemia	1 (11.1%)	0	0.28
New arrhythmia	0	2 (8.7%)	>0.99
Urinary retention	0	2 (8.7%)	>0.99
TIA	0	1 (4.3%)	>0.99
Diarrhea	0	1 (4.3%)	>0.99

Analysis B: Adjusted Outcomes

The effect of the medication groups on continuous variable outcomes was assessed using linear regression analysis to control for significantly different baseline characteristics. Regression results are shown in Table B4. One patient in the Propofol plus midazolam group had a LOS of 32 days and was excluded as an outlier (shown previously in Fig. 4). Compared to the Propofol only group, Propofol plus midazolam was not associated with LOS (Coefficient 0.2 days, 95%CI: [-0.5, 0.8], p = 0.62), change in creatinine (Coefficient -0.02 mg/dL, 95%CI: [-0.2, 0.1], p = 0.85), change in hemoglobin (Coefficient -0.06 g/dL, 95%CI: [-0.5, 0.7], p = 0.64), or creatinine at discharge (Coefficient -0.04 mg/dL, 95%CI: [-0.3, 0.2], p = 0.76). Conversely, other variables in the model were significantly association with several outcomes. First, a 1% increase in STS Risk Score was associated with a 0.13 day increased in LOS (Coefficient 0.13 days, 95%CI: [0.05, 0.2], p = 0.002). Second, a 1 kg/m^2 increase in body mass index (BMI) was associated with a 0.015 mg/dL increase in creatinine post-operatively (Coefficient 0.015 mg/dL, 95%CI: [0.003, 0.03], p = 0.016) and a 0.028 mg/dL increase in discharge creatinine (Coefficient 0.028 mg/dL, 95%CI: [0.008, 0.048], p = 0.007).

Table B4 - Propofol plus midazolam vs. Propofol only
Linear Regression Analyses

Regression Outcome	Variable	Coefficient	95% CI	P Value
Hospital length of stay (days) (1 outlier removed from Propofol plus midazolam group)	*Propofol plus midazolam (versus Propofol only)*	*0.169*	*-0.506, 0.843*	*0.62*
	Age	0.021	-0.019, 0.062	0.31
	BMI	0.003	-0.048, 0.055	0.90
	STS Risk Score	0.126	0.047, 0.206	**0.002** *
	Atrial fibrillation	-0.095	-0.666, 0.476	0.74
	Prior myocardial infarction	-0.278	-0.919, 0.364	0.39
	Treated with Remifentanil	0.459	-0.309, 1.226	0.24
	Fentanyl Dose (mcg/kg/hr)	-0.575	-1.783, 0.633	0.35
Change in Creatinine, pre to	*Propofol plus midazolam*	*-0.016*	*-0.177, 0.145*	*0.85*
	Age	-0.0002	-0.010, 0.010	0.96

post-procedure (mg/dL)	BMI	0.015	0.003, 0.028	**0.016 ***
	STS Risk Score	0.011	-0.008, 0.030	0.25
	Atrial fibrillation	-0.052	-0.189, 0.085	0.46
	Prior myocardial infarction	0.048	-0.105, 0.202	0.53
	Treated with Remifentanil	0.009	-0.175, 0.193	0.92
	Fentanyl Dose (mcg/kg/hr)	0.029	-0.259, 0.317	0.84
Change in Hemoglobin, pre to post-procedure (g/dL)	*Propofol plus midazolam*	*0.063*	*-0.526, 0.652*	*0.83*
	Age	-0.026	-0.062, 0.010	0.16
	BMI	-0.027	-0.073, 0.0182	0.24
	STS Risk Score	0.035	-0.035, 0.105	0.33
	Atrial fibrillation	0.326	-0.176, 0.827	0.20
	Prior myocardial infarction	0.004	-0.558, 0.566	0.99
	Treated with Remifentanil	-0.546	-1.220, 0.129	0.11
	Fentanyl Dose (mcg/kg/hr)	0.002	-1.053, 1.057	0.99
Creatinine at discharge (mg/dL)	*Propofol plus midazolam*	*-0.040*	*-0.304, 0.224*	*0.76*
	Age	-0.004	-0.020, 0.012	0.61
	BMI	0.028	0.008, 0.048	**0.007 ***
	STS Risk Score	0.028	-0.004, 0.059	0.08
	Atrial fibrillation	0.030	-0.195, 0.255	0.79
	Prior myocardial infarction	-0.047	-0.299, 0.204	0.71
	Treated with Remifentanil	-0.007	-0.312, 0.298	0.96
	Fentanyl Dose (mcg/kg/hr)	-0.133	-0.606, 0.339	0.58

Logistic regression analysis was used to assess for association between Propofol plus midazolam and binary outcomes of interest. Regression results are shown in Table B5. Propofol plus midazolam was not significantly associated with post-operative PPM (Odds Ratio 1.0, 95%CI: [0.3, 3.1], p = 0.94) or with RBC transfusion (OR 1.2, 95%CI: [0.3, 5.0], p = 0.83). 18 patients had pre-operative permanent PPMs and were excluded from the analysis of post-operative PPM (n=4, 5.7% and n=14, 14.9%, p = 0.08, Table B1). However, there was a significant association between STS Risk Score and post-operative RBC transfusion (OR 1.2, 95%CI: [1.05, 1.40], p = 0.008). Additionally, STS Risk Score was associated with increased odds of LOS $\geq$ 4 days (OR 1.21, 95%CI: [1.07, 1.34], p = 0.004, Table B5).

Table B5 - Propofol plus midazolam vs. Propofol only
Logistic Regression Analyses

Outcome	Variable	Odds Ratio	95% CI	P Value
Post-operative PPM, excluding pre-existing PPM (n= 164)	*Propofol plus midazolam (versus Propofol only)*	*1.041*	*0.336, 3.137*	*0.94*
	Age	0.990	0.928, 1.059	0.76
	BMI	1.044	0.962, 1.134	0.30
	STS Risk Score	0.977	0.830, 1.113	0.76
	Atrial fibrillation	0.843	0.305, 2.192	0.73
	Prior myocardial infarction	1.049	0.330, 3.007	0.93
	Treated with Remifentanil	1.068	0.262, 3.677	0.92
	Fentanyl Dose (mcg/kg/hr)	0.732	0.091, 4.996	0.76
RBC transfusion	*Propofol plus midazolam*	*1.176*	*0.256, 5.023*	*0.83*
	Age	1.019	0.936, 1.118	0.67
	BMI	1.065	0.950, 1.196	0.28
	STS Risk Score	1.205	1.054, 1.401	**0.008 ***
	Atrial fibrillation	0.400	0.093, 1.414	0.18
	Prior myocardial infarction	1.333	0.314, 4.983	0.68
	Treated with Remifentanil	3.818	0.894, 15.93	0.063
	Fentanyl Dose (mcg/kg/hr)	0.499	0.030, 6.330	0.61
Length of stay ≥ 4 days (Prolonged LOS)	*Propofol plus midazolam (versus Propofol only)*	*0.845*	*0.279, 2.417*	*0.78*
	Age	1.012	0.947, 1.085	0.73
	BMI	0.983	0.904, 1.067	0.69
	STS Risk Score	1.205	1.068, 1.377	**0.004 ***
	Atrial fibrillation	0.550	0.210, 1.359	0.21
	Prior myocardial infarction	0.422	0.112, 1.283	0.16
	Treated with Remifentanil	2.460	0.842, 7.027	0.09
	Fentanyl Dose (mcg/kg/hr)	0.285	0.033 2.035	0.23
Hypotension (amongst patients with prolonged LOS, n=9 versus n=23) †	*Propofol plus midazolam (versus Propofol only)*	*5.790*	*0.632, 81.60*	*0.14*
	Age	0.920	0.790, 1.056	0.23
	BMI	0.940	0.740, 1.148	0.56
	STS Risk Score	0.842	0.592, 1.065	0.25
	Atrial fibrillation	0.236	0.011, 2.091	0.24
	Prior myocardial infarction	0.636	0.009, 22.73	0.82

† Input variables for Remifentanil treatment and Fentanyl dose were removed, because the model did not converge.

Cox proportional hazard analysis found no association between the Propofol plus midazolam group and mortality compared to the Propofol only group (Hazard Ratio 0.5, 95%CI: [0.2, 1.2], p = 0.13). Other variables did demonstrate significant association with mortality: 1% increase in STS Risk score was associated with a 12% increase in hazard of

death (HR 1.12, 95%CI: [1.0, 1.2], p = 0.003), and atrial fibrillation was associated with a 128% increase in hazard of death (HR 2.28, 95%CI: [1.1, 4.8], p = 0.03).

Table B6 - Propofol plus midazolam vs. Propofol only
Cox Proportional Hazard Model Outcomes

Outcome	Variable	Hazard Ratio	95% CI	P Value
Mortality	*Propofol plus midazolam*	0.510	*0.212, 1.226*	*0.13*
	Age	1.049	0.991, 1.111	0.10
	BMI	1.031	0.962, 1.104	0.39
	STS Risk Score	1.120	1.039, 1.206	**0.003** *
	Atrial fibrillation	2.277	1.079, 4.801	**0.03** *
	Prior myocardial infarction	0.935	0.413, 2.117	0.87
	Treated with Remifentanil	1.148	0.461, 2.862	0.77
	Fentanyl Dose (mcg/kg/hr)	0.566	0.107, 2.982	0.50

Analysis C: Dexmedetomidine versus No Dexmedetomidine

Lastly, the 272 CS patients were divided into the *Dexmedetomidine group* (n=86) and the *No Dexmedetomidine group* (n=186). Patient characteristics are reported in Table C1. The groups only differed significantly in incidence of peripheral arterial disease, where the Dexmedetomidine group had significantly more disease burden (26.7% versus 13.4%; p = 0.01). Additionally, the case distribution over time differed significantly between the groups (p < 0.0001, Fig. 7), indicating that the procedure year needs to be taken into account as a potential confounding variable.

Table C1 - Dexmedetomidine vs. No Dexmedetomidine group
Baseline Characteristics of TAVR Patients

	Dexmedetomidine (n=86)	No Dex (n=186)	P Value
Age (years)	82.3 ± 8.7	83.0 ± 8.0	0.52
Male sex	46 (53.5%)	107 (57.5%)	0.60
BMI (kg/m^2)	27.6 ± 6.2	28.5 ± 5.6	0.28
STS Risk of Mortality Score	6.4 ± 4.0	6.2 ± 4.1	0.72
Hypertension	74 (87.2%)	157 (84.4%)	0.59
Diabetes	34 (39.5%)	62 (33.3%)	0.34
Currently on dialysis	4 (4.7%)	2 (1.1%)	0.08
Peripheral arterial disease	23 (26.7%)	25 (13.4%)	**0.01** *

Cerebrovascular disease/TIA	8 (9.3%)	17 (9.1%)	>0.99
Prior Stroke	11 (12.8%)	12 (6.5%)	0.10
Immunocompromised	8 (9.3%)	23 (12.4%)	0.54
Chronic lung disease	13 (15.1%)	32 (12.7%)	0.73
Current or former smoker	51 (59.3%)	113 (60.8%)	0.89
Home oxygen	6 (7.0%)	7 (3.8%)	0.36
Atrial fibrillation	26 (30.2%)	71 (38.2%)	0.22
Atrial flutter	5 (5.8%)	8 (4.3%)	0.56
Conduction defect	27 (31.4%)	51 (27.4%)	0.56
Permanent pacemaker	14 (16.3%)	24 (12.9%)	0.46
Diseased coronary vessels - none	36 (41.9%)	81 (43.5%)	0.30
Diseased coronary vessels - 1	15 (17.4%)	48 (25.8%)	
Diseased coronary vessels - 2	18 (20.9%)	31(16.7%)	
Diseased coronary vessels - 3	17 (19.8%)	26 (13.4%)	
Diseased proximal LAD	24 (27.9%)	53 (28.5%)	>0.99
Diseased left main coronary artery	12 (14.0%)	15 (8.1%)	0.13
Prior myocardial infarction	22 (25.6%)	46 (24.7%)	0.88
Prior PCI	28 (32.6%)	66 (35.5%)	0.68
Prior coronary artery bypass	27 (31.4%)	39 (21.0%)	0.07
NYHA Class II	14 (16.3%)	31 (16.7%)	0.23
NYHA Class III	66 (76.7%)	129 (69.4%)	
NYHA Class IV	6 (7.0%)	26 (14.0%)	
Prior aortic valve replacement	5 (5.8%)	16 (8.6%)	0.48
Elective procedure	82 (95.3%)	171 (91.9%)	0.44
Urgent procedure	4 (4.7%)	15 (8.1%)	
No anginal symptoms	75 (87.2%)	156 (83.9%)	0.73
Angina, NSTEMI, STEMI	3 (3.5%)	10 (5.4%)	
Likely non-ischemic symptoms	8 (9.3%)	20 (10.8%)	
Pre-procedure hemoglobin (g/dL)	12.1 ± 1.9	11.8 ± 1.8	0.30
Pre-procedure creatinine (mg/dL)	1.2 ± 1.0	1.2 ± 0.7	0.63
Pre-procedure platelets (per μL)	221k ± 85k	205k ± 91k	0.18

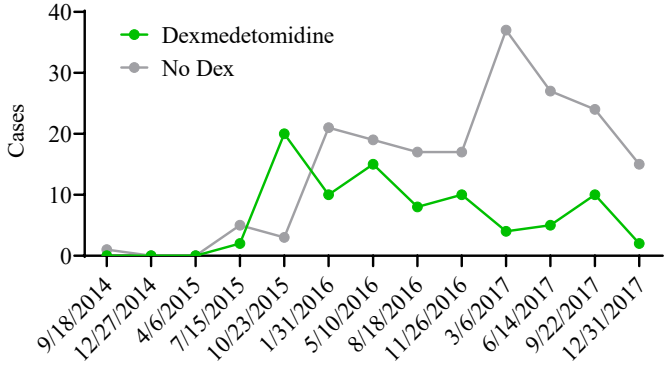

Figure 7: TAVR Cases over time, Dexmedetomidine versus No Dexmedetomidine. The distributions of cases over time significantly different (Kolmogorov-Smirnov test, p <0.0001).

Procedural characteristics are presented in Table C2. Cutdown access occurred in both groups (2.3% versus 1.1%, p = 0.59). Several other procedural characteristics were significantly different: fewer patients in the Dexmedetomidine group were treated with

propofol (50% versus 88.2%, p <0.0001) and remifentanil (13.3% versus 40.6%, p <0.0001), and propofol doses were significantly lower in the Dexmedetomidine group (mean dose 0.76 mcg/kg/hr versus 1.1 mcg/kg/hr, p = 0.0024, Fig. 8).

Table C2 – Dexmedetomidine vs. No Dexmedetomidine group
Summary Statistics of TAVR Procedural Characteristics

	Dexmedetomidine (n=86)	No Dex (n=186)	P Value
Valve-in-valve procedure	4 (4.7%)	10 (5.4%)	>0.99
Percutaneous Access	84 (97.7%)	184 (98.9%)	0.59
Cutdown Access	2 (2.3%)	2 (1.1%)	
Treated with propofol	43 (50%)	164 (88.2%)	**<0.0001 ***
Propofol dose (mg/kg/hr)	0.76 ± 0.7	1.1 ± 0.7	**0.006 ***
Treated with midazolam	25 (29.1%)	74 (39.8%)	0.10
Midazolam dose (mcg/kg/hr)	6.7 ± 3.5	7.1 ± 4.0	0.70
Treated with dexmedetomidine	86 (100%)	0	-
Dexmedetomidine dose (mcg/kg/hr)	0.40 ± 0.2	-	-
Treated with fentanyl	68 (79.1%)	162 (87.1%)	0.10
Fentanyl dose (mcg/kg/hr)	0.41 ± 0.3	0.42 ± 0.2	0.08
Treated with remifentanil	13 (15.1%)	42 (22.6%)	0.19
Remifentanil dose (mcg/kg/hr)	1.7 ± 1.3	1.8 ± 1.4	0.94

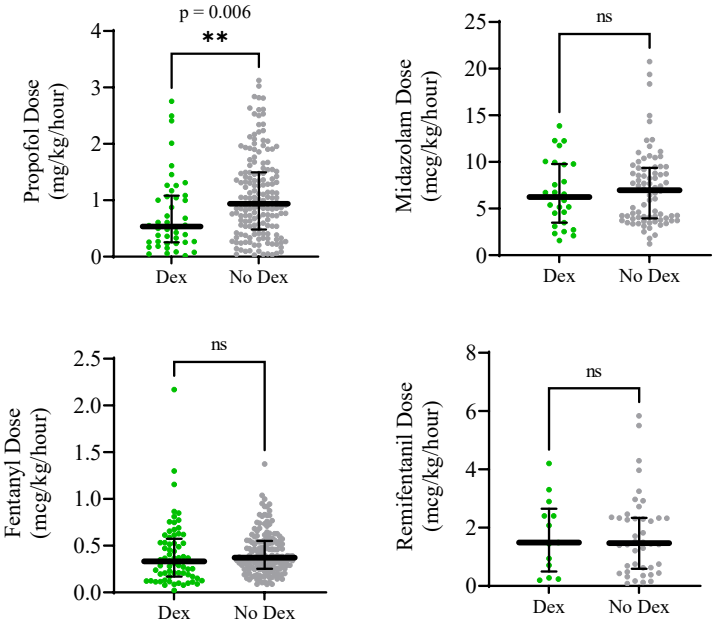

Figure 8: Comparison of medication doses between the Dexmedetomidine versus No Dexmedetomidine groups. The Kolmogorov-Smirnov test was used to compare doses. ns, not significant; Dex, Dexmedetomidine.

Analysis C: Unadjusted outcomes

Unadjusted procedure outcomes are shown in Table C3a. Total anesthesia time did not differ significantly between the groups (204 minutes versus 198, p = 0.25). No patients were converted to GA in the Dexmedetomidine group, and 2 were converted in the No Dexmedetomidine group (p > 0.99). There was no difference in in-hospital mortality (1.2% versus 0.5%, p = 0.53) or in discharge location (81.4% discharged to home or nursing home versus 81.4%, p > 0.99). There was also no difference in the percent of patients who experienced prolonged LOS (23.3% versus 19.9%, p = 0.53, Table C3b), and there were no differences in the incidence of specific causative complications.

Table C3a – Dexmedetomidine vs. No Dexmedetomidine
Unadjusted, Descriptive Statistics of Peri- and Postoperative Outcomes

	Dexmedetomidine (n=86)	**No Dexmedetomidine (n=186)**	**P Value**
Total anesthesia time (minutes)	204 ± 48	198 ± 40	0.25
Conversion to general anesthesia	0	2 (1.1%)	>0.99
Conversion to surgical replacement	0	0	-
Procedure aborted	0	0	-
Deceased in-hospital	1 (1.2%)	2 (1.1%)	>0.99
Discharged to hospice	0	2 (1.1%)	-
Discharged to home or nursing home	70 (81.4%)	149 (80.1%)	>0.99
Discharged to rehab/extended care/transitional care unit	15 (17.4%)	34 (18.3%)	

Table C3b – Dexmedetomidine vs. No Dexmedetomidine (Patients with LOS ≥ 4 days)
Unadjusted, Descriptive Statistics of Postoperative Complications

	Dexmedetomidine (n=20)	**No Dexmedetomidine (n=37)**	**P Value**
Incidence of LOS ≥ 4 days	20 (23.3%)	37 (19.9%)	0.53
Hypotension	4 (20%)	11 (29.7%)	0.54
Fluid overload	9 (45%)	10 (27.0%)	0.24
Elevated creatinine	3 (15%)	7 (18.9%)	>0.99
Heart block	6 (30%)	11 (29.7%)	>0.99
PPM Placement	6 (30%)	10 (27.0%)	>0.99
Infection	3 (15%)	7 (18.9%)	>0.99
Stroke	1 (5%)	3 (8.1%)	>0.99
Bleeding	5 (25%)	8 (21.6%)	0.75

Hypertension	1 (5%)	2 (5.4%)	>0.99
Delirium	3 (15%)	2 (5.4%)	0.33
New arrhythmia	3 (15%)	2 (5.4%)	0.33
Pseudogout	1 (5%)	0	0.35
Diarrhea	1 (5%)	1 (2.7%)	>0.99
Urinary retention	0	3 (8.1%)	0.54
TIA	0	1 (2.7%)	>0.99
Limb ischemia	0	1 (2.7%)	>0.99

Analysis C: Adjusted Outcomes

Linear regression was used to assess for association between the Dexmedetomidine group and continuous variable outcomes. Results are show in Table C4. One patient in the No Dexmedetomidine group had a LOS of 32 days and was excluded as an outlier (shown previously in Fig. 4). Inclusion in the Dexmedetomidine group was not significantly associated with hospital LOS (Coefficient -0.1 days, 95%CI: [-0.9, 0.6], p = 0.71, Table C4), post-operative change in creatinine (Coefficient -0.01 mg/dL, 95%CI: [-0.1, 0.1], p = 0.84), post-operative change in hemoglobin (Coefficient -0.2 g/dL, 95%CI: [-0.7, 0.2], p = 0.35), or creatinine at discharge (Coefficient -0.01 mg/dL, 95%CI: [-0.2, 0.2], p = 0.93). Conversely, peripheral arterial disease was associated with an increase in discharge creatinine (Coefficient 0.5 mg/dL, 95%CI: [0.3, 0.7], p = <0.0001).

Table C4 - Dexmedetomidine vs. No Dexmedetomidine
Linear Regression Analyses

Regression Outcome	Variable	Coefficient	95% CI	P Value
Hospital length of stay (days) (one outlier excluded from the No Dex group)	*Dexmedetomidine (versus No Dexmedetomidine)*	*-0.145*	*-0.917, 0.626*	*0.71*
	Peripheral arterial disease	0.195	-0.661, 1.052	0.65
	Procedure Year	-0.055	-0.551, 0.441	0.83
	Propofol Dose, mg/kg/hr	-0.276	-0.717, 0.164	0.22
Change in Creatinine, pre to post-procedure (mg/dL)	*Dexmedetomidine*	*-0.012*	*-0.134, 0.109*	*0.84*
	Peripheral arterial disease	0.096	-0.039, 0.231	0.16
	Procedure Year	-0.037	-0.115, 0.041	0.35
	Propofol Dose, mg/kg/hr	0.009	-0.061, 0.078	0.81
	Dexmedetomidine	*-0.216*	*-0.675, 0.243*	*0.35*

Change in Hemoglobin, pre to post-procedure (g/dL)	Peripheral arterial disease	0.094	-0.415, 0.604	0.72
	Procedure Year	-0.147	-0.442, 0.149	0.33
	Propofol Dose, mg/kg/hr	0.060	-0.203, 0.322	0.65
Creatinine at discharge (mg/dL)	*Dexmedetomidine*	*-0.010*	*-0.233, 0.214*	*0.93*
	Peripheral arterial disease	0.498	0.250, 0.746	**<0.0001 ***
	Procedure Year	0.019	-0.125, 0.163	0.80
	Propofol Dose, mg/kg/hr	-0.013	-0.141, 0.115	0.85

Table C5 shows results of logistic regression analysis. The Dexmedetomidine group had no significant association with incidence of post-operative PPM (Odds Ratio 0.8, 95%CI: [0.3, 1.9], p = 0.51, Table C1) or with RBC transfusion (OR 0.5, 95%CI: [0.1, 1.6], p = 0.25). 38 patients had pre-existing PPMs and were excluded from the PPM analysis (n=14, 16.3% and n=24, 12.9%, Table C1). Finally, cox proportional hazard analysis found no association between the Dexmedetomidine group and mortality (Hazard Ratio 1.0, 95%CI: [0.6, 1.9], p = 0.82, Table C6).

Table C5 - Dexmedetomidine vs. No Dexmedetomidine
Logistic Regression Analyses

Regression Outcome	Variable	Odds Ratio	95% CI	P Value
Post-operative PPM, excluding pre-existing PPM (n= 234)	*Dexmedetomidine (versus No Dexmedetomidine)*	*0.781*	*0.307, 1.911*	*0.59*
	Peripheral arterial disease	1.080	0.372, 2.747	0.88
	Procedure Year	0.991	0.563, 1.797	0.98
	Propofol Dose, mg/kg/hr	0.899	0.525, 1.483	0.68
RBC transfusion	*Dexmedetomidine*	*0.511*	*0.148, 1.557*	*0.25*
	Peripheral arterial disease	1.638	0.430, 5.156	0.42
	Procedure Year	1.690	0.794, 3.979	0.20
	Propofol Dose, mg/kg/hr	0.476	0.196, 0.998	0.07

Table C6 - Dexmedetomidine vs. No Dexmedetomidine
Cox Proportional Hazard Model Outcomes

Regression Outcome	Variable	Odds Ratio	95% CI	P Value
Mortality	*Dexmedetomidine*	*1.071*	*0.603, 1.903*	*0.82*
	Peripheral arterial disease	1.146	0.607, 2.163	0.68
	Procedure Year	1.000	0.999, 1.000	0.57
	Propofol Dose, mg/kg/hr	0.790	0.550, 1.133	0.20

DISCUSSION

TAVR has rapidly become a common treatment for severe, symptomatic AS, and more TAVR procedures are being completed under CS instead of GA than ever before.[24] Despite growing popularity of CS or Monitored Anesthesia Care (MAC; CS administered by an anesthesiologist) in TAVR, there has been limited investigation into the optimal MAC medications for TAVR patients. The current study retrospectively analyzed outcomes after TAVR for three different medication group comparisons: *Propofol versus No Propofol* (Analysis A), *Propofol plus midazolam versus Propofol* only (Analysis B), and *Dexmedetomidine versus No Dexmedetomidine* (Analysis C). The study found that for each analysis, the medication group had no significant association with total hospital LOS, mortality, and need for PPM. Additionally, there were no significant differences between the groups in each analysis for secondary outcomes of interest, including: in-hospital death, discharge location, change in creatinine from pre- to post-procedure, change in hemoglobin from pre- to post-procedure, creatinine at discharge, and need for post-operative RBC transfusion.

The lack of significant association between MAC medication and outcomes is consistent with previous findings from Khalil et al.,[40] Mayr et al.,[41] Chen et al.,[42] and Kronfli et al.[43] Each of these prior studies found no difference in post-operative outcomes between the comparator medication groups (propofol-opioid vs. dexmedetomidine; propofol vs. propofol plus dexmedetomidine; or propofol only vs. dexmedetomidine only). However, the lack of difference in these and the current study does not rule out the possibility that a certain MAC regimen is truly associated with better or worse outcomes

after TAVR. It is possible that a difference does exist but has not been detected due to small sample sizes and low frequency of events, resulting in underpowered analyses.

Results from the current study do indicate that it is possible that propofol plus midazolam may be suboptimal for TAVR compared to propofol only. In Analysis B, the Propofol plus midazolam group had greater incidence of hypotension as a causative factor of prolonged LOS, although the increase in incidence was not significant in unadjusted analysis (55.5% versus 17.4%, p = 0.075, Table B3) or in adjusted analysis (Odds Ratio 5.79, 95%CI: [0.63, 81.6], p = 0.14, Table B5). This is of interest despite lack of significance, because the Propofol plus midazolam group had a larger percentage of patients affected by hypotension leading to prolonged LOS despite having a younger and less ill cohort than the Propofol only group. This regimen notably combines two medications known to synergize and to cause cardiovascular depression, and propofol plus midazolam has been associated with worse outcomes in other procedures; in a randomized study comparing outcomes for endoscopy patients treated with propofol only (n=120) versus propofol plus midazolam (n=119), propofol plus midazolam resulted in significantly longer recovery time and a significantly lower recovery quality (based on patient scoring), despite achieving similar efficacy of intra-operative sedation.[48] Therefore, this study indicates further exploration of the effects of propofol plus midazolam versus propofol only in MAC for TAVR may be warranted. It is possible that with a greater sample size, the association between Propofol plus midazolam and post-operative hypotension could become significant.

Some of the baseline patient characteristics did vary significantly between the groups in each analysis. The variation was very likely due to the lack of randomization and

retrospective nature of this study. First, patients in the Propofol group had fewer pre-existing permanent pacemakers (11% versus 23%, p = 0.02, Table A1). Anesthetic agents are not expected to negatively affect the function of PPMs,[67] but propofol has potential to be pro-arrhythmic by blocking or drastically slow conduction. It is possible that providers may have avoided propofol in patients with pacemakers due to this potentially pro-arrhythmic effect, but the literature linking propofol to increased risk of arrhythmias is mixed and lacking.[52] Patients in the Propofol group were also less likely to have had left main coronary disease (8% versus 17%, p=0.054, Table A1). This association was likely because providers were wary of the effects of propofol on cardiac function and hemodynamic in patients with coronary artery disease (CAD). Propofol has been shown to reduce systolic and diastolic blood pressure, myocardial blood flow, and myocardial oxygen consumption in CAD patients.[68-70]

Next, patients in the Propofol plus midazolam group were younger (78.8 year ± 8.3 versus 85.9 years ± 6.0, p <0.0001, Table B1) and had lower STS risk score (5.3 ± 3.7 versus 6.4 ± 5.3, p = 0.04, Table B1). It is possible that the association of the Propofol plus midazolam group with age and STS Risk Score is due to providers preferring to use a combination of synergistic medications in younger, potentially less sedation-sensitive patients. It is recognized that co-administration of propofol and midazolam results in increased sedative and cardio-respiratory depression effects of both medications,[33,34] with the combination resulting in deeper sedation and more frequent deep sedation than propofol alone.[22,44] It is also recognized that elderly patients are more sensitive to both propofol[71,72] and midazolam,[73] and it is sensible that providers would avoid this exposure.

Lastly, more patients treated in the Dexmedetomidine group had prior peripheral arterial disease (PAD, 26.7% versus 13.4%, p = 0.01, Table C1). This may be due to institutional or provider preference, since choice of MAC medications used in patients with PAD does not have strict guidelines.[74] Kronfli et al. also had a dexmedetomidine group with significantly more patients with prior PAD than the propofol group (78.6% versus 72.7%, p = 0.024), but this difference is not explained.[43] There may be some advantage to use of dexmedetomidine over midazolam for patients with PAD; in a randomized study treated PAD patients with either dexmedetomidine plus remifentanil or midazolam plus remifentanil, patients treated with dexmedetomidine had significantly lower post-operative pain scores and higher satisfaction.[75]

There were differences in the doses of other MAC medications received in each group. First, patients in the Propofol group (Analysis A) received less dexmedetomidine (20.7% versus 65.6%, p <0.0001, Table A2) and less remifentanil (13.3% versus 40.6%, p <0.0001, Table A2) than patients in the No Propofol group. This is expected, because the propofol group will have received propofol, reducing the need for other medications to achieve adequate sedation. Similarly, patients in the Propofol plus midazolam group (Analysis B) received less remifentanil (8.6% versus 22.3%, p = 0.02, Table B2) compared to patients in the Propofol only group. However, the Propofol plus midazolam group received more fentanyl than the Propofol only group (0.52 ± 0.2 mcg/kg/hr versus 0.35 ± 0.2 mcg/kg/hr, p = 0.0002, Table B2). This is possibly because fewer Propofol plus midazolam patients received remifentanil overall (8.6% versus 22.3%), so there were more patients in the group who received fentanyl as the only opioid. It is possible that patient who otherwise would have also received remifentanil received a higher dose of fentanyl

instead, raising the group mean dose. Lastly, fewer patients in the Dexmedetomidine group (Analysis C) were treated with propofol (50% versus 88.2%, $p < 0.0001$, Table C2), indicating that patients given dexmedetomidine may need and receive less propofol to attain adequate sedation.

Even though the studied CS medication groups were ultimately not associated with outcomes of interest, other variables that were included in the regression analyses were significantly associated with outcomes. In Analysis B, STS Risk score was associated with a 0.13 day increased in LOS (Coefficient 0.13 days, 95%CI: [0.05, 0.2], $p = 0.002$, Table B4) and an increased hazard of post-operative mortality (Hazard Ratio 1.12, 95%CI: [1.04, 1.21], $p = 0.003$, Table B6). Both of these associations are expected, since STS Risk Score is intentionally designed to predict outcomes including length of hospital stay and mortality after valve replacement.[76] STS Risk score was also independently associated with an increase in post-operative blood transfusion (Odds Ratio 1.21, 95%CI: [1.05, 1.40], $p = 0.008$, Table B5). Need for post-TAVR transfusion is commonly due to intraprocedural vascular damage and complications leading to blood loss during and after the procedure.[77] It is possible that increase in STS Risk score leads to increased transfusion, because patients with higher scores are sicker and may be more susceptible to vascular injury and less resilient due to comorbidities and frailty.

In Analysis B, BMI was independently associated with an increase in creatinine before versus after the TAVR (Coefficient 0.015 mg/dL, 95%CI: [0.003, 0.028], $p = 0.016$, Table B4) and with an increase in creatinine at discharge (Coefficient 0.028 mg/dL, 95%CI: [0.008, 0.048], $p = 0.007$, Table B4). This can be explained by previous evidence showing that increased patient BMI is associated with increased risk of acute kidney injury

after surgery and a greater post-procedural increase in creatinine.[78-80] Additionally in Analysis B, atrial fibrillation was independently associated with mortality (Hazard Ratio 2.3, 95%CI: [1.08, 4.8], p = 0.03, Table B6). This corroborates findings that patients with atrial fibrillation suffer from an increased risk of all-cause mortality compared to the general population.[81,82] Lastly, in Analysis C, PAD was associated with an increase in discharge creatinine (Coefficient 0.5 mg/dL, 95%CI: [0.25, 0.75], p < 0.0001, Table C4). The increase in creatinine is likely secondary to perioperative renal hypoperfusion due to vascular disease. Indeed, PAD is a risk factor for acute kidney injury following surgery.[83,84]

This study has several key limitations. First, this is a retrospective study, so biases in patient selection and distribution to MAC groups were not controlled for. Indeed, there were noted differences in baseline characteristics. Multivariate regression should have helped account for these differences, although it is still possible that unknown variables may have confounded the effects of recorded variables. Additionally, study data is limited by what was recorded accurately in the chart. Next, this analysis did not take into account patient ASA score (I-VI), which may have contributed to provider decision-making in choosing a MAC regimen. Next, the sample size for the current study was still relatively small, and effects of medication groups may be hidden by underpowered analyses. The sample sizes were limited by heterogeneity of medication combinations used in the surveyed sample. Lastly, Analysis A and Analysis C were comparisons of aggregate groups, meaning patients in the Propofol group for Analysis A could also have been treated with dexmedetomidine or midazolam. While the analysis accounted for frequency and dose of other medications to control for this additional variable, this adjustment may not have fully accounted for potential drug synergies.

In this single institution patient population, MAC medication group was not significantly associated with outcomes of interest, including total hospital LOS, mortality, and need for post-operative PPM. These findings suggest that within MAC, specific medication choice may not significantly affect clinically impactful outcomes after TAVR. However, it is still possible that a difference exists and requires a larger cohort to be detected. Further investigation is warranted, because even small improvements in outcomes related to MAC medications could be magnified and generate tangible gains in quality and cost of TAVR patient care. In particular, testing of propofol plus midazolam versus propofol only or midazolam only is warranted, because propofol plus midazolam may prolong recovery and resulting hospital LOS due to synergistic cardiovascular depressant effects.

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